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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,873	01/19/2001	Hongsheng Su	104385-132	9057

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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/766,873	SU ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *23-25 and 27-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,26 and 30-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 January 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Notice of References Cited	Application/Control No. 09/766,873	Applicant(s)/Patent Under Reexamination SU ET AL.	
	Examiner Richard G Hutson	Art Unit 1652	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO 96/01894	01-1996	WIPO	Bennett et al.	-
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	McBride et al., Development of Techniques to Genetically Manipulate Members of the Genera Cytophaga, Flavobacterium, Flexibacter, and Sporocytophaga, Applied and Environmental Microbiology, Vol. 62, No. 8, pages 3017-3022, August 1996.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

DETAILED ACTION

Applicants preliminary amendment of claim 23 and the addition of new claims 30-34, Paper No. 7, 10/10/2002, is acknowledged. Claims 1-34 are still at issue and are present for examination.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-22, 26 and newly added claims 30-34, 26 in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the examination of Groups I-III, or at a minimum Groups I and II together, would not pose a serious burden on the examiner. Applicants submit that Group I is directed to a host cell itself, while Group II is directed to a method of using the host cell to make a desired polypeptide and Group III is directed to vectors which express gene products and are designed to be used in the host cells. Applicants submit that as such, a search for prior art involving the host system and method of using the system would not pose an undue burden and that examination of the method of making and using the same product is further supported by 35 U.S.C. 103(b) wherein biotechnological processes of making and using nonobvious products are deemed allowable upon an indication of allowability of the product claims.

Applicants argument is not found persuasive because while the searches for the each of the groups overlap, they are not coextensive. For example, search of Group II would require search of subclass 435/69.1 and search of Group III would require search

of subclass 435/320.1. A search of each of these subclasses would be unnecessary the search of the elected group I. Further applicants are reminded that group I is currently drawn to the bacterial species *Flavobacterium heparinum*, both transformed and untransformed.

The requirement is still deemed proper and is therefore made FINAL.

Claims 23-25 and 27-29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 7

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Priority

Applicants claim of the benefit of U.S. Provisional application 60/177,568, filed 1/21/2000, is acknowledged.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosures, Paper No. 4, filed 5/7/2001, and Paper No. 5, filed 10/15/2001, is acknowledged. Those references considered have been initialed.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Drawings

The drawings are objected to because the specification contains two sets of different drawings. That is to figures labeled 1 and two figures labeled 2. Each of the different figures, 1 and 2, while being similar are not identical. The figure set in which both Figure 1 and 2 are on the same sheet of paper, as opposed to the other Figure 1 and 2, which are on individual sheets, has been accepted and have been approved by the draftsperson. Some indication as to which set of figures is correct is needed.

Specification

The disclosure is objected to because of the following informalities: Because the specification contains two sets of figures as discussed above under Drawings.

Appropriate correction is required.

Claim Objections

Claims 7 is objected to because of the following informalities:

Claims 7 recites "wherein a gene **encoded** by said integrated DNA is expressed at high levels.". Genes are not encoded, but rather genes encode proteins. It is suggested that applicants amend this recitation such as "wherein said integrated DNA comprises a gene which is expressed at high levels."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-22, 26 and 30-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (2-22, 26 and 30-34 dependent on) are indefinite in that it is drawn to a host cell "for recombinant DNA expression" comprising a *Flavobacterium heparinum*. The phrase "for recombinant DNA expression" is an intended use of the claimed host cell and has no patentable weight with respect to the claimed product, which is a host cell comprising a *Flavobacterium heparinum*. Thus, claim 1 is reasonably interpreted as a host cell comprising a *Flavobacterium heparinum*.

Claim 4 is indefinite in that it is unclear what applicants intend to be encompassed by a "modified broad-host plasmid". Specifically what are the metes and bounds of those broad-host plasmids considered to be "modified".

Claim 12 is indefinite in that it is unclear what applicants intend to be encompassed by a "heparinase I gene regulatory region". Specifically what are the metes and bounds of the group of regulatory regions considered to be encompassed by a "heparinase I gene regulatory region".

Claim 22 is indefinite in that it is unclear what applicants intend to be encompassed by a "*hepA*". Specifically what are the metes and bounds of the group of promoters considered to encompassed by a "*hepA*" promoter.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22, 26 and 30-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-22, 26 and 30-34 are directed to all possible transformed *Flavobacterium heparinum* host cells comprising any vector (claims 1, 2, 5-22, 26 and 30-34), wherein said vector is any broad-host plasmid (claims 3 and 4). This rejection is applied to the above claims based on the interpretation that claim 1 is interpreted as "a transformed *Flavobacterium heparinum* host cell for recombinant DNA expression" (See above 112 2nd paragraph rejection). The specification only provides a single representative species of transformed *Flavobacterium heparinum* host cells (i.e.

transformed with pIBFX1 and pIBFX2) encompassed by these claims. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-22, 26 and 30-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *Flavobacterium heparinum* transformed with pIBFX1 and pIBFX2, does not reasonably provide enablement for a *Flavobacterium heparinum* transformed with any vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-22, 26 and 30-34 are so broad as to encompass any *Flavobacterium heparinum* host cells comprising any vector (claims 1, 2, 5-22, 26 and 30-34), wherein said vector is any broad-host plasmid (claims 3 and 4). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely vectors broadly encompassed by the claims. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the vector with which Flavobacterium heparinum is transformed. Since the nucleic acid sequence of a vector determines its structural and functional properties, predictability of which changes can be tolerated in a vector's nucleic acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which nucleic acids in the vector's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the vector's structure relates to its function. However, in this case the disclosure is limited to that *Flavobacterium heparinum* transformed with pIBFX1 and pIBFX2.

The specification does not support the broad scope of the claims which encompass all modifications of any vector because the specification does not establish: (A) regions of the vector structure which may be modified without effecting its activity; (B) the general tolerance of any vector to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleic acid residue of any vector with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation

that would be required to determine which substitutions would be acceptable to retain the desired activity claimed and the fact that the relationship between the sequence of a vector and its function (i.e. its activity) are not well understood and are not predictable, it would require undue experimentation for one skilled in the art to arrive at the majority of those transformed *Flavobacterium heparinum* of the claimed genus.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any *Flavobacterium heparinum* transformed with any vector. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5-8 and 13-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Zimmerman et al. (WO 96/01894, January 25, 1996).

Zimmerman et al. teach the culturing of the gram negative organism, *Flavobacterium heparinum*, and the isolation and cloning of the genes encoding the enzymes, chondroitinase AC and chondroitinase B, from *Flavobacterium heparinum*. Thus claims 1, 5-8 and 13-18 are anticipated by Bennett et al. (See above 112 2nd paragraph rejection).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11, 13-21, 26 and 30-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman et al. (WO 96/01894, January 25, 1996) and McBride et al. (Applied and Environmental Microbiology, Vol. 62, No. 8, pages 3017-3022, August 1996).

As discussed above, Zimmerman et al. teach the culturing of the gram negative organism, *Flavobacterium heparinum*, and the isolation and cloning of the genes encoding the enzymes, chondroitinase AC and chondroitinase B, from *Flavobacterium heparinum*. Zimmerman et al. further teach that the cloned genes can be used in conjunction with suitable expression systems to produce the enzymes in

Flavobacterium, for example, under the control of overexpression promoters, or in organisms other than *Flavobacterium*.

McBride et al. the development of techniques to genetically manipulate members of the genera *Flavobacterium*. McBride et al. teach that Tn4351 transposon DNA can be transferred from *E. coli* to *Flavobacterium meningosepticum*.

One of ordinary skill in the art at the time of filing would have been motivated to express the genes encoding the *Flavobacterium heparinum* enzymes, chondroitinase AC and chondroitinase B, in *Flavobacterium heparinum* under the control of an overexpression promoter in a suitable expression system, such as the tn4351 transposon DNA, as taught by McBride et al., and suggested above by Bennett et al. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes and sequences. Bennett et al. teach the sequence and isolation of the chondroitinase AC and chondroitinase B genes themselves and the McBride et al. teaches the tn4351 expression system which they successfully used to introduce heterologous DNA into *Flavobacterium meningosepticum*. The art also teaches many methods of the introduction of such expression systems into the host cell such as conjugation, electroporation and phage transfection. The advantages of such recombinant production include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by overexpressing the protein, thus decreasing the relative level of naturally

occurring contaminants of the protein. The reasonable expectation of success comes from the results of McBride et al. who successfully used the tn4351 transposon to introduce heterologous DNA into *Flavobacterium meningosepticum.* Thus claims 1-11, 13-21, 26 and 30-34 are made obvious by Bennett et al. and McBride et al.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
December 11, 2002